Cerebral Injury After Cardiac Surgery
Identification of a Group at Extraordinary Risk

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Background and Purpose—Cerebral injury after cardiac surgery is now recognized as a serious and costly healthcare problem mandating immediate attention. To effect solution, those subgroups of patients at greatest risk must be identified, thereby allowing efficient implementation of new clinical strategies. No such subgroup has been identified; however, patients undergoing intracardiac surgery are thought to be at high risk, but comprehensive data regarding specific risk, impact on cost, and discharge disposition are not available.

Methods—We prospectively studied 273 patients enrolled from 24 diverse US medical centers, who were undergoing intracardiac and coronary artery surgery. Patient data were collected using standardized methods and included clinical, historical, specialized testing, neurological outcome and autopsy data, and measures of resource utilization. Adverse outcomes were defined a priori and determined after database closure by a blinded independent panel. Stepwise logistic regression models were developed to estimate the relative risks associated with clinical history and intraoperative and postoperative events.

Results—Adverse cerebral outcomes occurred in 16% of patients (43/273), being nearly equally divided between type I outcomes (8.4%; 5 cerebral deaths, 16 nonfatal strokes, and 2 new TIAs) and type II outcomes (7.3%; 17 new intellectual deterioration persisting at hospital discharge and 3 newly diagnosed seizures). Associated resource utilization was significantly increased—prolonging median intensive care unit stay from 3 days (no adverse cerebral outcome) to 8 days (type I; \( P<0.001 \)) and from 3 to 6 days (type II; \( P<0.001 \)), and increasing hospitalization by 50% (type II, \( P=0.04 \)) to 100% (type I, \( P<0.001 \)). Furthermore, specialized care after hospital discharge was frequently necessary in those with type I outcomes, in that only 31% returned home compared with 85% of patients without cerebral complications (\( P<0.001 \)). Significant risk factors for type I outcomes related primarily to embolic phenomena, including proximal aortic atherosclerosis, intracardiac thrombus, and intermittent clamping of the aorta during surgery.

For type II outcomes, risk factors again included proximal aortic atherosclerosis, as well as a preoperative history of endocarditis, alcohol abuse, perioperative dysrhythmia or poorly controlled hypertension, and the development of a low-output state after cardiopulmonary bypass.

Conclusions—These prospective multicenter findings demonstrate that patients undergoing intracardiac surgery combined with coronary revascularization are at formidable risk, in that 1 in 6 will develop cerebral complications that are frequently costly and devastating. Thus, new strategies for perioperative management—including technical and pharmacological interventions—are now mandated for this subgroup of cardiac surgery patients. (Stroke. 1999;30:514-522.)

Key Words: cardiopulmonary bypass | cerebral embolism and thrombosis | coronary heart disease | postoperative complications

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*See Appendix I for a complete list of the investigators and centers.

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Cerebral injury complicating cardiac surgery is recognized as a critical healthcare problem for the estimated 1 million patients undergoing cardiac surgery annually throughout the world. The 6% incidence recently found for stroke and severe intellectual dysfunction after coronary artery bypass graft (CABG) surgery is most likely attributable to macroemols of air or particulate matter, with risk increasing due to aging of this population. Attention is now focused on the identification of subgroups of cardiac surgery patients who are most likely to develop such complications, thereby allowing a more effective approach to this problem. A group thought to warrant specific attention is patients undergoing open-heart procedures, such as aortic or mitral valve replacement or repair. These patients commonly present with intracardiac thrombus or valve vegetation and often entrap air within the cardiac chambers intraoperatively, all of which appear to increase the risk of cerebral embolization and subsequent injury. However, only single center experiences or retrospective reviews exist. Furthermore, almost no data exist for patients undergoing combined intracardiac and coronary procedures who may be at extremely high risk.

Because more than 200 000 open-chamber procedures are performed annually throughout the world, including approximately 100 000 combined procedures, we designed a large-scale, prospective, multicenter observational study to determine the magnitude of this problem, to identify patient subsets and other markers of risk, and to assess impact on mortality, resource utilization, and long-term disposition.

Subjects and Methods
The Multicenter Study of Perioperative Ischemia (McSPI) Cardiac Surgery Study is a prospective observational study that enrolled 2417 cardiac surgery patients from 24 US medical institutions (see Appendix I). After institutional board approval, at each center, between 100 and 108 patients were prospectively enrolled according to a systematic and randomized sampling scheme. Randomization and sampling were based on CABG surgery caseload at each institution. Therefore, there was some variation from site to site in the proportion of patients who actually had an intracardiac procedure.

Intraoperative demographic, clinical, and laboratory data were collected using a standardized Case Report form that included approximately 1500 data fields per patient addressing the period from hospital entry to discharge. A total of 297 patients underwent a left-sided intracardiac procedure combined with CABG surgery; of these, 24 patients had concurrent carotid endarterectomy and were excluded from the analysis. Of the 273 remaining patients, 136 (50%) underwent aortic valve replacement, 77 (28%) mitral valve replacement or repair, and 60 (22%) other procedures (24 left ventricular aneurysctomy, 18 proximal aortic procedures, 15 combined aortic and mitral valve repairs and replacements, and 3 isolated atrial or ventricular septal defect repairs).

Demographic data, perioperative clinical information, 12-lead electrocardiograms, and laboratory data were collected prospectively and recorded on the standardized Case Reports by a site investigator (a dedicated nurse or physician participant) who had undergone specific training and used a study operation manual. Additionally, CT and MR data for stroke confirmation, electroencephalographic data for seizure confirmation, autopsy data for death classification, and hospital discharge data for patient disposition were assimilated. After the database was locked, all data were reviewed for each patient, and neurological outcomes were determined by a 6-member end point committee chaired by the senior neurologist (S.H.G.). Each member reviewed all data independently with final decisions made by consensus. Two categories of outcome were prospectively defined: Type I—as death due to stroke or hypoxic encephalopathy, new nonfatal stroke, or transient ischemic attack (TIA), or stupor or coma at the time of discharge; and type II—as a new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or a nonmetabolic seizure without evidence of focal injury. Patients with more than 1 type of neurological outcome were hierarchically classified as a single outcome, according to severity, with type I outcomes considered more severe than type II.

Potential predictors of neurological outcome (Appendix II) were categorized according to operative stage as preoperative (eg, age, gender, a history of congestive heart failure, or prior CABG surgery), intraoperative (eg, the duration of cardiopulmonary bypass and aortic cross-clamping, surgical and anesthetic techniques, hemodynamic changes, surgical assessment of proximal aortic atherosclerosis), and postoperative (eg, myocardial infarction, dysrhythmia, ventricular dysfunction) events occurring on the day of surgery. Resource utilization was assessed on the basis of (1) the postoperative length of stay in intensive care units; (2) the total postsurgical stay in the hospital; and (3) the site to which the patient was discharged—home versus intermediate-care facility versus long-term care facility.

Statistical Analysis
Univariate associations between potential predictors (Appendix II) and adverse neurological outcome, type I or type II, were assessed with either Fisher’s exact test or Kruskal-Wallis test, as appropriate. Then, stepwise logistic regression was performed separately for type I and type II outcomes and included predictors associated with a value of $P \leq 0.20$ from the univariate analyses (Table 1). Our final models for type I and type II cerebral outcomes included only those predictors associated with adverse cerebral outcome with a significance level of $P \leq 0.05$. Results are reported as odds ratios with associated 95% confidence intervals.

Results
Demographic, historical and operative characteristics of the 273 patients studied are presented in Table 1. Patients were elderly (mean age, 70 ± 9 years) and had a history of hypertension, with a sizable number having diabetes mellitus, obesity, and female gender. Nearly 1 in 7 patients had a history of cerebrovascular disease, including stroke or TIA. The durations of cardiopulmonary bypass (166 ± 68 minutes) and aortic cross clamping (105 ± 41 minutes) were somewhat long, reflecting relatively complex surgery combining intracardiac and coronary artery surgeries.

Cerebral Outcomes
Forty-three of the 273 patients, or 15.8%, developed 1 or more new postoperative adverse cerebral outcomes. Twenty-three patients, or 8.4%, developed a type I outcome—including 5 patients with fatal strokes, 16 with nonfatal strokes, and 2 with TIAs. Twenty other patients, or 7.3%, developed a type II outcome—including 17 with a new deterioration in intellectual function and 3 with seizures in the absence of focal injury.

Using predictors identified by univariate analysis for both types of outcome (Table 1), logistic regression identified 3 principal predictors of type I cerebral outcome, all related to the presence or manipulation of atherosclerotic plaque or thrombus (Table 2). Of note, a 5-fold increase in risk of a type I outcome was found for patients with moderate to severe proximal aortic atherosclerosis, as assessed clinically by palpation of the aorta by the cardiac surgeon before cannulation. Intracardiac thrombus directly detected during surgery...
and the use of multiple intermittent cross-clamping of the aorta independently increased risk, whereas a history of myocardial infarction was weakly associated with the absence of type I outcome. Type II cerebral outcomes also were associated with proximal aortic atherosclerosis. However, other factors were uniquely associated with type II outcomes, including a history of endocarditis, postoperative conditions associated with a low-output state such as myocardial infarction or heart failure, a history of alcohol abuse, and perioperative dysrhythmia. In patients with a history of hypertension, elevated systolic blood pressure at hospital admission (>145 mm Hg) was a risk factor, whereas those with well-controlled blood pressures appeared to be at reduced risk.

Because age was considered to be a potentially important predictor of outcome, we included this variable in the final model for type I and type II cerebral outcomes. Although point estimates vary slightly, reflecting the association between age and the presence of proximal aortic atherosclerosis, our final model results did not change (Table 2). Four patients died within 24 hours of surgery, and cause of death could not be ascertained, therefore mandating (by protocol) classification as no neurological outcome. We also analyzed the data with these patients excluded, and our findings did not change.

### Resource Utilization and Cost

Patients with type I outcome, but not type II outcome, were 4 times more likely to die during hospitalization (Table 3). The mean duration of postoperative stay in the intensive care unit was increased by 1 week for both type I and type II outcomes, and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence of Type I Outcome (n=23)</th>
<th>Incidence of Type II Outcome (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence of Characteristic in All Patients, %</td>
<td>In Patients With Characteristic, %</td>
</tr>
<tr>
<td>Age &gt;70 years¶</td>
<td>51.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Body mass index &gt;28 kg/cm²#</td>
<td>29.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Gender: female</td>
<td>32.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Medical history*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>14.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>16.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>29.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Hypertension#</td>
<td>61.0</td>
<td>7.6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>65.9</td>
<td>7.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>40.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2.6</td>
<td>20.0</td>
</tr>
<tr>
<td>Prior CABG surgery</td>
<td>13.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Prior valve surgery</td>
<td>9.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>9.3</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>21.9</td>
<td>13.0</td>
</tr>
<tr>
<td>Anti-hypertensive medication</td>
<td>41.0</td>
<td>10.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>51.2</td>
<td>7.9</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>44.0</td>
<td>13.9</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>14.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Intraoperative factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal aortic atherosclerosis</td>
<td>30.4</td>
<td>18.6</td>
</tr>
<tr>
<td>Ventricular or atrial thrombus</td>
<td>7.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Intermittent cross-clamp</td>
<td>4.4</td>
<td>36.4</td>
</tr>
<tr>
<td>Perioperative dysrhythmia</td>
<td>35.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Postoperative factors†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.3</td>
<td>0</td>
</tr>
</tbody>
</table>

¶Variable with 1 missing value.

#Variable with 4 missing values.

†These conditions were assessed in the intensive care unit on the day of surgery.

*History of carotid disease includes carotid bruit or stenosis. Alcohol abuse consumption indicates hospitalization because of alcohol consumption or alcohol withdrawal. Perioperative dysrhythmias were defined as the occurrence of moderate to severe arrhythmia after cardiopulmonary bypass or dysrhythmia on the day of surgery. CABG denotes coronary artery bypass graft.
median stay increased by more than 2-fold for both outcomes when compared with patients without adverse neurological outcomes (but including those who had nonneurological complications).

In these patients without adverse neurological outcomes, postoperative hospital stay averaged 15 days, with 85% of surviving patients returning home. However, patients with type I outcomes who survived had an average hospital stay of 1 month, with less than one third of them returning home. For patients with type II outcomes, hospital stay was prolonged by 1 week compared with patients without adverse cerebral events, with 75% of type II patients returning home.

**Discussion**

This multicenter prospective investigation assessed cerebral complications in 273 patients undergoing coronary revascularization plus a left-sided intracardiac procedure, a combination currently performed more than 100,000 times per year in the United States. Sixteen percent of these patients suffered a postsurgical neurological injury, equally divided between fatal and nonfatal strokes (type I outcome), and clinically detectable deterioration in intellectual function (type II outcome). Compared with those patients who did not have an adverse neurological outcome, patients suffering Type I outcome had a 4-fold increase in hospital mortality, a 1-week increase in intensive care unit stay, and a 2-week increase in overall hospitalization. Furthermore, more than two thirds of these patients were not discharged to their homes but rather to chronic care or rehabilitation facilities. Also noteworthy was the fact that type II outcomes were associated with a significant increase in intensive care unit and hospitalization stays and with a trend toward increased need for chronic care facilities.

**Previous Studies**

The problem of perioperative neurological morbidity associated with myocardial revascularization has recently been demonstrated to be serious and costly; therefore, identification of those patients at highest risk is mandated. Based on a number of single-center observational studies, 1 such subgroup may be those undergoing an intracardiac procedure, such as valve repair or replacement. In fact, risk may be even higher in these patients than after myocardial revascularization alone (most recently reported to be 6% across multiple centers). In both intracardiac and extracardiac surgery, the preponderance of evidence suggests that macroemboli (greater than 200 μm in diameter) as well as microemboli (less than 40 μm) are responsible for most neurological complications. Macroemboli (associated with atherosclerotic plaque disruption) are believed to precipitate focal defects, whereas particulate microemboli (consisting of white cell and platelet aggregates, fat, or air) may be implicated in more subtle diffuse cerebral dysfunction.

Regarding solid emboli, risk appears to increase with age due to the associated increase in prevalence and complexity of atherosclerotic plaque.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Model for Type I* Cerebral Outcome (n=23)</th>
<th>Model for Type II† Cerebral Outcome (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Venticular or atrial thrombus</td>
<td>11.3</td>
<td>(2.5, 50.6)</td>
</tr>
<tr>
<td>Intermittent aortic cross-clamping</td>
<td>7.2</td>
<td>(1.6, 32.3)</td>
</tr>
<tr>
<td>Proximal aortic atherosclerosis</td>
<td>4.7</td>
<td>(1.8, 12.3)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>0.3</td>
<td>(0.1, 0.8)</td>
</tr>
<tr>
<td>History of endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative congestive heart failure or myocardial infarction (on day of surgery)</td>
<td>26.0</td>
<td>(1.5, 437.2)</td>
</tr>
<tr>
<td>History of alcohol abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative dysrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated admission/preoperative systolic blood pressure among chronic hypertensive patients (uncontrolled hypertension)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal admission/preoperative systolic blood pressure among chronic hypertensive patients (controlled hypertension)§</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Type I: goodness of fit value equals 2.3 with 4 degrees of freedom (P=.68). Area under the receiver operating characteristic curve (“c” index) is 0.80.
†Type II: goodness of fit value equals 5.0 with 7 degrees of freedom (P=.66). Area-under-the-receiver operating characteristic curve (“c” index) is 0.90.
‡Adjusted odds ratio among the type I and type II cerebral outcomes vs that among the patients without adverse neurological outcome.
§These last 2 factors are included because of the significant interaction between admission/preoperative systolic blood pressure (SBP) and chronic hypertension. Elevated SBP is defined as SBP >145 mm Hg. Chronic hypertension is defined as a history of hypertension or preadmission/preoperative use of antihypertensive medications.
Adverse Cerebral Outcomes After Intracardiac Surgery

TABLE 3. Mortality, Resource Utilization and Long-term Disposition

<table>
<thead>
<tr>
<th>Neurological Outcome</th>
<th>Type I Outcome</th>
<th>Type II Outcome</th>
<th>No Adverse Cerebral Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=23)</td>
<td>(n=20)</td>
<td>(n=230)</td>
</tr>
<tr>
<td>Mortality (in-hospital), % (n)</td>
<td>30.4 (7)</td>
<td>5.0 (1)</td>
<td>7.4 (17)</td>
</tr>
<tr>
<td>Resource utilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of intensive care unit stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.3 (17.5)</td>
<td>11.8 (18.6)</td>
<td>5.0 (7.3)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>7.7 (1.2, 82.6)</td>
<td>6.0 (0.8, 83.8)</td>
<td>2.9 (0.0, 68.9)</td>
</tr>
<tr>
<td>Duration of postoperative hospital stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.6 (27.5)</td>
<td>22.7 (26.9)</td>
<td>15.4 (20.6)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>24.2 (2.5, 107.3)</td>
<td>14.5 (7.2, 125.1)</td>
<td>11.0 (0.6, 228.8)</td>
</tr>
<tr>
<td>Discharge to home, % (n/N)</td>
<td>31 (5/16)</td>
<td>74 (14/19)</td>
<td>85 (180/213)</td>
</tr>
</tbody>
</table>

* Patients without adverse cerebral events, but may have nonneurological complications (eg, cardiac, renal, infections).
† Among surviving patients (N).

Thus, our study has now demonstrated that the magnitude of injury in these patients is far greater than previously believed, effectively mandating immediate attention to this subgroup.

Predictors of Type I Outcome

Moderate to severe proximal aortic atherosclerosis, as assessed clinically, occurred in 30% (83/273) of all patients, most notably in patients suffering type I outcome (13/23). The predictive value may have been even higher had more sensitive technologies for determination of atherosclerotic disease been used, such as ultrasonic scanning using transesophageal or epicardiac echocardiography.22–25 We also found that repeated aortic cross-clamping, which is not an uncommon practice, was a risk factor.26 Our results are consistent with studies in which transcranial Doppler echocardiography was used, demonstrating that emboli most commonly occur during aortic cannulation, clamping, unclamping, and creation of the proximal vein graft anastomoses.27–30 Thus, we advise against both repeated aortic occlusion and occlusion in an area of moderate to severe atherosclerosis. Current surgical management should be changed in these circumstances, either by altering the site of aortic cannulation and anastomoses,24,31 by using only arterial grafts (such as internal mammary arteries), or by inducing hypothermic fibrillatory arrest. Finally, for extreme cases, even the more radical approach of resection and subsequent graft replacement of the severely atherosclerotic aorta, using hypothermic circulatory arrest, should be considered.31–33

Regarding intracardiac thrombus, approximately 20% of our patients with thrombus developed a type I outcome. Supportive of this finding are the results of several smaller studies suggesting that left atrial or ventricular clot or thrombus is associated with cerebral injury.6,8,10 Certainly, our finding is not unexpected given the substantial manipulation of the heart, particularly to achieve surgical exposure in these patients.27–29
A history of myocardial infarction was associated with a decreased incidence of type I outcome, which may be explained by our finding of an interaction between myocardial infarction and pharmacological therapy for myocardial infarction, which included use of antithrombotic agents, therapies that may in fact provide protection from type I cerebral outcomes. However, we were unable to discern a statistically significant association between these therapies and type I outcomes most likely because of the relatively small sample size.

Predictors of Type II Outcomes
Type II outcomes occurred nearly as frequently as type I and most likely reflect higher cortical level dysfunction. A number of contributory factors to such an injury have been suggested, including diffuse microembolic obstruction of small capillaries or arterioles, effects of excitotoxic and inflammatory mediators, cerebral hypoperfusion, and cerebral hyperthermia induced during rewarming. In support of a microembolic etiology, we found that moderate to severe proximal aortic atherosclerosis was a significant risk factor for type II outcome, as was a history of endocarditis (most likely predisposing to dislodgement of valvular calcification or vegetation).34 The association of type II outcomes with perioperative dysrhythmias, congestive heart failure, and myocardial infarction implicate hypoperfusion and intracardiac thrombus formation as causes of injury. Although elevated admission systolic blood pressure was a risk factor, hypertensive patients whose pressures were well-controlled at admission had fewer adverse cerebral outcomes. Perhaps antihypertensive medications are neuroprotective. Our finding that alcohol abuse was associated with cognitive dysfunction, but not stroke, may be related to exacerbation of an underlying alcoholic encephalopathy or even the acute effects of alcohol withdrawal, both of which can be exacerbated by cardiac surgery and cardiopulmonary bypass.

Strengths and Limitations of This Study
Previous studies in surgical populations have reported incidences of perioperative stroke varying by more than 10-fold—from less than 0.5% to more than 5%.2–8,11,13,18,35–39 This variability may be explained by differences in study design (retrospective versus prospective), sample size, methodology, and site-specific factors.2,3,35,36,40–42 Our study design addresses these limitations by including multiple diverse

**TABLE 4. Comparison of Patients Undergoing a Combined Procedure vs CABG Only**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Combined Procedure (n=273)†</th>
<th>CABG Only (n=2108)†</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.0±9.0</td>
<td>63.9±10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>32.6</td>
<td>22.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.7±15.5</td>
<td>81.2±15.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neurological disease</td>
<td>14.6%</td>
<td>8.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22.1%</td>
<td>25.1%</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61.0%</td>
<td>57.2%</td>
<td>0.26</td>
</tr>
<tr>
<td>Proximal aortic atherosclerosis (moderate-severe)</td>
<td>30.4%</td>
<td>12.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>166.2±67.5</td>
<td>102.6±38.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>105.3±40.7</td>
<td>57.4±24.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type I event</td>
<td>8.4%</td>
<td>3.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type II event</td>
<td>7.3%</td>
<td>3.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Any CNS event</td>
<td>15.8%</td>
<td>6.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No CNS event</td>
<td>7.4% (17/230)</td>
<td>1.9% (38/1979)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type I event</td>
<td>30.4% (7/23)</td>
<td>21.2% (14/66)</td>
<td>0.54</td>
</tr>
<tr>
<td>Type II event</td>
<td>5.0% (1/20)</td>
<td>9.5% (6/63)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.
*For continuous variables, the mean±standard deviation are displayed; otherwise, values displayed are percentages.
†For the combined procedure, the number of patients (n) = 273, with the following exception: age (n=272); cardiopulmonary bypass time (n=271); hypertension (n=269); aortic cross clamp time (n=269). For CABG the number of patients (n) = 2108 with the following exceptions: age (n=2107); weight (n=2104); cardiopulmonary bypass time (n=2076); hypertension (n=2057); aortic cross clamp time (n=2034).
institutions (university and private hospitals, specialized cardiac surgery clinics, federal centers, and health maintenance organizations), which, in effect, minimized practice or site-specific factors. Also, limiting the period of the study to the same 24-month period in all participating institutions and randomizing enrollment allowed us to mitigate any effect of changes in practice. Finally, all data were collected prospectively, and outcomes were assessed by an independent and blinded panel.

There are, however, several limitations of this study. First, our sample size may be too small to discern several associative relationships between predictors and outcomes, as well as borderline findings. Perhaps for the same reason, no site-related effects were identified, eg, hospital type or cardiac surgical caseload. Nevertheless, our study is the largest prospective multicenter investigation of this cardiac surgical subpopulation. Second, neurological examinations were performed by investigators at each site and not by a single neurologist at all institutions. However, all clinical findings were assessed before any analysis, in a blinded fashion by an independent panel. Also, when neurological examination findings were questionable, CT or MRI was performed. A third limitation is that we did not assess cognitive function using neuropsychological (psychometric) testing to discern more subtle changes in mentalation and behavior. Such testing requires laborious assessment, over prolonged periods, and was not within the scope of our study. However, based on the 2.5-fold increase in overt cerebral injury that we found in our patients, compared with CABG patients, neuropsychological assessment of this high-risk population appears to be a worthwhile endeavor. Another limitation is that we detected aortic atherosclerosis by surgical palpation and not by the more sensitive technique of ultrasonography, which was not always available or considered to be a standard of care at the time this study was performed. However, surgical palpation, when positive for identification of ascending aortic atherosclerotic disease, is quite unmistakable and specific. At a minimum, this technique should be universally applied, because it is easy to perform, is cost-free, and now is of proven importance. A final limitation is that although we were able to make comparisons between patients undergoing CABG surgery only and patients undergoing combined procedures in prospective studies, we were not able to compare these groups to patients undergoing intracardiac surgery only (eg, valve surgery without CABG), because these patients were not previously studied by our research group. Such a comparison would be an important area for future investigation.

Summary

This multicenter prospective study is the first to identify a subgroup of cardiac surgery patients at extraordinary risk of cerebral injury. These patients, who were undergoing combined intracardiac and revascularization procedures, suffered overt cerebral injury commonly—in 1 out of every 6 patients—resulting in prolonged intensive care, in-hospital stays, and an increased need for long-term specialized care. Given that more than 200 000 patients worldwide undergo open-chamber procedures annually, of which approximately 100 000 are combined with CABG, we estimate that annually 15 000 to 30 000 patients will suffer such serious cerebral events. Our study also identified patients and surgical characteristics that conferred added risk, including the presence of aortic atherosclerotic plaque, intracardiac thrombus, and cardiac vegetation. These findings indicate a change in current practice (including more aggressive presurgical assessment of intra-aortic plaque and intracardiac thrombus) and the use of alternative surgical techniques to minimize embolic injury. Finally, we believe that our results mandate investigation of new methods for mitigating cerebral injury in this very high-risk population, including strategies for prevention (new paradigms for management of intra-aortic plaque and control of cerebral reperfusion temperature) and acute intervention (specific cerebral protective agents).

Appendix I


The following institutions and persons participated in the McSPI EPI-I study. Centers and investigators: University of Alabama at Birmingham—W. Lell; Baylor College of Medicine—S. Shenaq, R. Clark; Cedars-Sinai Medical Center, Calif—A. Friedman; University of Chicago—M. Trankina, W. Ruo; Cleveland Clinic Foundation—C. Koch, N. Starr; Correll University—O. Patafio, R. Fine; Duke University—T. Stanley, M. Newman; Emory University—C. Mora Mangano, J. Ramsay; Harvard University: Beth Israel Hospital—M. Comunale; Brigham and Women’s Hospital—S. Body, R. Maddi; Massachusetts General Hospital—M. D’Ambra; University of Iowa—A. Ross; Kaiser-Permanente Medical Center, San Francisco—G. Roach, W. Bellows; University of Michigan—J. Wahr; New York University—M. Kanchuger, K. Marschall; University of Pennsylvania—J. Savino; Rush Presbyterian, St. Luke’s Medical Center—K. Tuman; Stanford University—E. Stover, L. Siegel; Texas Heart Institute—S. Slogoff; M. Goldstein; Milwaukee Veterans Administration Medical Center—A. Aggarwal; San Francisco Veterans Administration Medical Center—G. Oranne; D. Mangano; Medical College of Virginia, Virginia Commonwealth University—J. Fabian, R.L. Wolman; University of Washington—B. Spiess; Yale University—J. Mathew.

Appendix II

Demographic Variables

Age in years as continuous and discrete variables (<65, 65–75, >75 years)

Gender

Height

Weight

Body mass index (BMI)=(weight in kg)/(height in meters)^2 as a continuous variable

Obesity defined as BMI >28

Hospital stay

Death

Prior Medical and Prior Surgical Variables

History of cigarette smoking

History of alcohol use defined as a history of heavy drinking, hospitalization for alcoholism, or alcohol withdrawal

Preoperative neurological status defined as prior stroke or TIA
Preoperative mental status defined as preoperative stupor, coma, confusion, disorientation, memory deficit, or speech deficit and no prior stroke or TIA

History of hypertension

History of myocardial infarction

History of unstable angina

History of pulmonary disease excluding pulmonary edema

Congestive heart failure defined by history of same or any 2 of the following positive findings on physical exam (jugular venous distention, rales, or S3 gallop)

Diabetes defined by history or pre-admission or preoperative use of insulin or oral hypoglycemic agents

History of dysrhythmia defined as atrial fibrillation or flutter, sick sinus syndrome, ventricular tachycardia, or fibrillation on admission, ventricular tachycardia or fibrillation requiring urgent or emergent surgery, or the pre-admission use of antiarrhythmics excluding digoxin and phenytoin

Renal insufficiency defined as a preoperative creatinine> 2 mg/dL or dialysis before admission

Valvular stenosis defined as aortic stenosis +/- mitral stenosis only defined by history of valvular disease, or other cardiac catheterization findings, or echocardiography findings

Valvular insufficiency defined as aortic insufficiency +/- mitral insufficiency only defined by history, or other cardiac catheterization findings, or echocardiography findings

History of endocarditis

Preoperative ejection fraction divided into the following groups determined by the highest recorded ejection fraction on ventriculography, radionuclear studies, or echocardiography: 0.40 (40%) by number or normal or mildly decreased 0.30–0.39 (30%–39%) by number or moderately decreased <0.30 (30%) by number or severely decreased

Admission systolic blood pressure >180 mm Hg on physical exam

Central vascular disease defined as a history of aortic aneurysm (abdominal or thoracic); +/-atherosclerosis (abdominal or thoracic); +/-or prior aortic vascular surgery (excluding renal and femoropopliteal)

Peripheral vascular disease defined as a history of peripheral vascular disease (arm +/-or leg)+/-or claudication; +/-or prior peripheral vascular surgery: +/-or prior aortic vascular surgery (femoropopliteal only)

Carotid vascular disease defined as a history of carotid disease (left or right); +/-or prior carotid endarterectomy (left +/-or right); +/-or carotid bruit (left +/-or right) on physical exam

Renal vascular disease defined as a history of renal vascular disease: +/-or prior aortic vascular surgery (renal only)

All vascular disease defined as central, peripheral, carotid, or renal vascular disease

History of prior coronary bypass graft (CABG) surgery

History of prior valve surgery

Redo surgery defined as a history of prior CABG surgery +/or prior valve surgery, +/or ascending or aortic arch vascular surgery

Aspirin use defined as regular use only, pre-admission, or preoperative use

Antihypertensives taken before admission or preoperatively

Beta-blockers taken before admission or preoperatively

Calcium channel blockers taken before admission or preoperatively

Emergency surgery defined as an electively scheduled procedure turned emergent

Preoperative and Intraoperative Variables

Thrombus defined as a history of myxoma or cardiac tumor, or atrial or ventricular thrombus on ventriculography or echocardiography, or atrial or ventricular thrombus noted by the surgeon

Cardiac index (CI) <1.5 L/m² per minute defined as a CI <1.5 L/m² per minute preoperatively on ventriculography or measured (CI <1.5 L/m² per minute; induction, pre-bypass, or post-bypass)

Intraoperative Variables

Proximal aortic atherosclerosis noted by the surgeon as moderate or severe

Hemodynamic inotropes defined as the pre-bypass or post-bypass use of inotropes other than routine

Cardiopulmonary bypass time in minutes

Aortic cross-clamp time in minutes

Intermittent cross-clamp use

Arterial filter use

Type of oxygenator: bubble or membrane

Difficulty with cannulation (hemorrhage, dissection, or air embolism only)

Ventricular ventilator use

Return to cardiopulmonary bypass

Intraoperative hypertension defined as a systolic blood pressure: >180 mm Hg on induction, pre-, or post-bypass; or mean arterial pressure >100 mm Hg on bypass

Intraoperative and/or Postoperative Variables

Perioperative hypotension defined as a systolic blood pressure <80 mm Hg on induction, pre-bypass, or post-bypass or mean arterial pressure <40 mm Hg on bypass, or systolic blood pressure <80 mm Hg or mean arterial pressure <40 mm Hg postoperatively on the day of surgery only

Perioperative dysrhythmia defined as a moderate or severe arrhythmia on induction, pre- or post-bypass; dysrhythmia on the day of surgery only

Hemodynamic assist device defined as the use of an intra-aortic balloon pump or other mechanical circulatory assist devices on the day of surgery only

Hematologic Variables

Preoperative hemoglobin/hematocrit (Hgb/Hct) low, defined as a preoperative Hgb <8 mg/dL or Hct <24%

Preoperative Hgb/Hct acceptable, defined as a preoperative Hgb >8 but <10 mg/dL; or Hct >24 but <30%

Preoperative Hgb/Hct normal, defined as a preoperative Hgb >=10 mg/dL or Hct >=30%

Intensive care unit (ICU) Arrival Hgb/Hct low, defined as Hgb <8 mg/dL or Hct <24%

ICU arrival Hgb/Hct acceptable, defined as Hgb >8 but <10 mg/dL; or Hct >24 but <30%

ICU arrival Hgb/Hct normal, defined as Hgb >=10 mg/dL or Hct >=30%

Postoperative Variables

Postoperative cardiac index <1.5 L/m² per minute on the day of surgery only

Postoperative cardiopulmonary resuscitation on the day of surgery only

Postoperative congestive heart failure on the day of surgery only

Postoperative valve dysfunction defined as embolism or valve dysfunction on the day of surgery only

Postoperative myocardial infarction on the day of surgery only

Postoperative vascular event, defined as an aortic dissection on the day of surgery only

Return to the operating room for hemorrhage, +/or tamponade, +/or valve dysfunction on the day of surgery only

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